REMARKS

Claims 70-120, 122, 123, 127-129, 135-137, 143-145, and 194-243 were withdrawn from issue and rejected. Claims 366 and 367 have been added herein. Thus, claims 70-120, 122, 123, 127-129, 135-137, 143-145, 194-243, and 366-367 are pending. Claims 70 and 122 have been amended herein to indicate that the recited mucoadministration is effective to reduce or eliminate the non-invasive fungus-induced rhinosinusitis and symptoms of the asthma. Claims 119 and 242 have been amended herein to indicate that the recited prophylactic mucoadministration is effective to prevent the non-invasive fungus-induced rhinosinusitis or symptoms of the asthma. Applicant's specification fully supports these amendments. For example, page 50, lines 16-19 disclose mucoadministering an antifungal agent to reduce or eliminate asthma symptoms. In addition, the section extending from page 50, line 29 to page 51, line 2 discloses mucoadministering an antifungal agent to prevent asthma symptoms. In addition, page 58, lines 19-24 disclose that the patients had non-invasive fungus-induced rhinosinusitis with allergic mucus. Thus, no new matter has been added.

In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 70-120, 122, 123, 127-129, 135-137, 143-145, 194-243, and 366-367.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 70 and 122 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for reducing asthma and non-invasive fungus-induced rhinosinusitis, does not reasonably provide enablement for eliminating said conditions.

Applicant respectfully disagrees. A person having ordinary skill in the art reading Applicant's specification would have been able to eliminate asthma and non-invasive fungus-induced rhinosinusitis as recited in previous claims 70 and 122 without undue experimentation.

To further prosecution, however, claims 70 and 122 have been amended to indicate that the recited mucoadministration is effective to reduce or eliminate the non-invasive fungus-induced rhinosinusitis and symptoms of the asthma.

Applicant's specification fully enables amended claims 70 and 122. In fact, Example 2 of Applicant's specification discloses treatment results for 53 human patients with non-invasive fungus-induced rhinosinusitis. As stated on page 59, lines 18-19, endoscopic evaluation revealed that 33 of the 53 patients went from stage 2 or 3 to stage 0 after three months. Stage 0 for endoscopic evaluation means "no evidence of disease." See, page 59, line 8. Thus, Applicant's specification provides no less than 33 working examples in human patients that demonstrate the elimination of non-invasive fungus-induced rhinosinusitis. Given these working examples, a person having ordinary skill in the art at the time Applicant filed certainly would have appreciated that the presently claimed methods can be used to eliminate non-invasive fungus-induced rhinosinusitis.

In addition, as disclosed on page 66, lines 15-19, 37 of the 53 human patients with non-invasive fungus-induced rhinosinusitis had previously diagnosed chronic asthma. After antifungal treatment, 28 of the 37 asthmatic patients "declared an improvement or complete elimination of asthma symptoms" upon questioning. Given these results, a person having ordinary skill in the art would have appreciated that symptoms of asthma can be eliminated using the presently claimed methods. Thus, a person having ordinary skill in the art reading Applicant's specification would have been able to practice the presently claimed invention without undue experimentation.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 70 and 122 under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 119, 120, 242, and 243 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating asthma and/or non-invasive fungus-induced rhinosinusitis, does not reasonably provide enablement for preventing/prophylaxis of said conditions.

Applicant respectfully disagrees. A person having ordinary skill in the art reading Applicant's specification would have been able to prevent asthma or non-invasive fungus-

induced rhinosinusitis as recited in previous claims 119, 120, 242, and 243 without undue experimentation.

To further prosecution, however, claims 119 and 242 have been amended to indicate that the recited prophylactic mucoadministration is effective to prevent the non-invasive fungus-induced rhinosinusitis or symptoms of the asthma. It is noted that claims 119 and 120 depend from claim 70, while claims 242 and 243 depend from claim 122. In addition, claims 119, 120, 242, and 243 recite prophylactically mucoadministering a prophylactic formulation in an amount, at a frequency, and for a duration effective to prevent the non-invasive fungus-induced rhinosinusitis or symptoms of the asthma after the mucoadminstration recited in either independent claim 70 or 122.

Applicant's specification fully enables present claims 119, 120, 242, and 243. In fact, Applicant's working examples demonstrate that the prophylactic mucoadministration, performed after the mucoadministration that resulted in treating non-invasive fungus-induced rhinosinusitis or asthma, prevented the return of non-invasive fungus-induced rhinosinusitis or the symptoms of asthma. For example, page 62, lines 13-15 of Applicant's specification discloses that:

> One patient stopped the nasal amphotericin B irrigations after two months. Eight months later that patient exhibited recurrent symptoms of the non-invasive fungus-induced rhinosinusitis condition.

In addition, page 70, lines 22-24 discloses that:

> Sometime after this patient's asthma symptoms improved, the patient stopped using the itraconazole irrigations. After four to six weeks of not using the itraconazole irrigations, the patient's asthma symptoms returned.

Thus, it is clear that a person having ordinary skill in the art would have appreciated that both non-invasive fungus-induced rhinosinusitis and symptoms of asthma can be prevented, once treated, using the presently claimed methods. Therefore, a person having ordinary skill in the art reading Applicant's specification would have been able to practice the presently claimed invention without undue experimentation.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 119, 120, 242, and 243 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 98 and 218 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asked for clarification with respect to how one liter of the formulation can be administered to a nostril.

Applicant respectfully submits that one liter of the formulation can be administered by nasal irrigation. For example, a syringe or bulb can be used to flush large amounts of an antifungal formulation through at least a portion of the nasal-paranasal anatomy. Applicant notes that most of the formulation that enters the nasal-paranasal anatomy upon irrigation exits the nostril. Thus, claims 98 and 218 are clear.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 98 and 218 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 70-75, 77, 88, 90-94, 104-108, 110-115, 119, 120, 143, and 145 under 35 U.S.C. § 102(b) as being anticipated by the Stankov reference (WO 96/00576), which published in German. It is noted that the Examiner referenced column and line numbers of U.S. Patent No. 5,880,101, which according to the Examiner is an English translation of the Stankov reference that appears to have an identical disclosure to that of the Stankov reference. Applicant has not verified whether or not the disclosure of U.S. Patent No. 5,880,101 is identical to that of the Stankov reference and reserves the right to comment on any differences should they exist.

The Examiner stated that the Stankov reference teaches "treating patients having the symptoms of asthma, allergic rhinitis, and sinusitis by daily oral administration of 1 g of nystatin (or amphotericin) for 6 months." According to the Examiner, this teaching is provided at column 41, lines 5-17.

Applicant respectfully disagrees. The Stankov reference does not anticipate the presently claimed invention. Column 41, lines 5-17 of U.S. Patent No. 5,880,101 discloses treating 15 patients with pollen allergies and 8 patients with dust allergies. At no point does this section, or any other section of U.S. Patent No. 5,880,101, disclose treating both non-invasive fungus-induced rhinosinusitis and the symptoms of asthma. In fact, column 41, lines 5-17 read as follows:

> b) 15 patients with pollen allergies and 8 patients with dust allergies were treated with daily oral doses of 1 g Nys for 6 months. Before commencement of therapy, the allergies of all patients had resisted treatment for at least 5 years or since birth. In all patients an almost complete disappearance of the symptoms (allergic rhinitis, asthma attacks, blocked nose, etc.) could be seen after 6 to 8 weeks. After discontinuance of therapy for experimental purposes (dechallenge) the symptoms slowly reappeared in about half the patients. After resumption of therapy (challenge) the symptoms could again be cured/improved.
>
> The same results were obtained in 7 patients with a corresponding Amp therapy.

A person having ordinary skill in the art reading this section would have appreciated that it does not disclose the successful treatment of both non-invasive fungus-induced rhinosinusitis and asthma. In fact, at no point does U.S. Patent No. 5,880,101 disclose treating a patient with sinusitis, let alone a patient with both non-invasive fungus-induced rhinosinusitis and asthma.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 70-75, 77, 88, 90-94, 104-108, 110-115, 119, 120, 143, and 145 under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 78-87, 96-103, 109, and 116-118 under 35 U.S.C. § 103(a) as being unpatentable over the Stankov reference (WO 96/00576). Specifically, the Examiner stated that the Stankov reference discloses "using nystatin or amphotericin for the treatment of asthma, allergic rhinitis and sinusitis." The Examiner then concluded that the "selection of optimal mode, amount and frequency of administration of nystatin or amphotericin for the

treatment of asthma, allergic rhinitis and sinusitis within the reference's generic disclosure, by routine experimentation, is obvious and within the skill of an ordinary practitioner."

Applicant respectfully disagrees. Proper analysis under 35 U.S.C. § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process; and (2) whether the prior art would also have revealed that in so carrying out, those of ordinary skill would have a reasonable expectation of success. See, In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

As stated above, U.S. Patent No. 5,880,101 discloses treating 15 patients with pollen allergies and 8 patients with dust allergies. See, column 41, lines 5-17. At no point does U.S. Patent No. 5,880,101 disclose treating a patient with sinusitis, let alone a patient with both non-invasive fungus-induced rhinosinusitis and asthma. In addition, at no point does U.S. Patent No. 5,880,101 teach or suggest that a person having ordinary skill in the art should treat a patient having both non-invasive fungus-induced rhinosinusitis and asthma. In fact, U.S. Patent No. 5,880,101 never mentions sinusitis, let alone non-invasive fungus-induced rhinosinusitis.

Even assuming for the sake of argument that U.S. Patent No. 5,880,101 somehow suggests that a person having ordinary skill in the art should treat a patient having both non-invasive fungus-induced rhinosinusitis and asthma, U.S. Patent No. 5,880,101 fails to provide a person having ordinary skill in the art with a reasonable expectation of success in achieving the successful treatment of such a patient. For example, U.S. Patent No. 5,880,101 does not provide any information regarding the successful treatment of patients with sinusitis, let alone patients with both non-invasive fungus-induced rhinosinusitis and asthma.

Taken together, it is clear that the cited art does not render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 78-87, 96-103, 109, and 116-118 under 35 U.S.C. § 103(a).

The Examiner also rejected claims 76, 89, 122, 123, 127-129, 135-137, 144, 194-214, and 216-243 under 35 U.S.C. § 103(a) as being unpatentable over the Stankov reference (WO 96/00576) in view of the Horner *et al.* reference (*Clinical Microbiology Reviews*, 8(2):161-179

(1995)) and the Bent and Kuhn reference (*Laryngoscope*, 106:1331-1334 (1996)). Specifically, the Examiner stated that (1) the Stankov reference teaches treating patients having allergies such as asthma, allergic rhinitis, and sinusitis by administration of nystatin or amphotericin and (2) the Horner *et al.* reference teaches that fungal spores are universal atmospheric components indoors and outdoors and are now generally recognized as important causes of respiratory allergies including asthma and rhinitis. The Examiner also stated that the Bent and Kuhn reference teaches diagnostic criteria for AFS including the presence of nasal polyps, fungal debris and eosinophilic mucus. In addition, the Examiner stated that the Bent and Kuhn reference teaches (1) that diagnosis of AFS can be done by nasal examination and (2) topical antifungal therapy of AFS by nasal postoperative irrigations. The Examiner concluded that:

> it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of treating allergic asthma, rhinitis and sinusitis of Stankov such that to include the step of identifying those patients that have fungal-induced rhinitis and sinusitis using the method described in Bent III et al. because of the widespread of fungal allergies as suggested by Horner et al. One having ordinary skill in the art would have been motivated to do this to obtain improved method of treatment of said fungal-induced rhinitis and sinusitis as suggested by Bent III et al.

With respect to claims 89 and 209, the Examiner stated that:

> Stankov does not teach the claimed azole compounds. However, Bent III et al. teach that ketaconazole was more effective than amphotericin and nystatin for the treatment of AFS. See p. 1333, Table III. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Stankov such that to employ ketaconazole in addition to or instead of nystatin or amphotericin for the treatment of asthma, allergic rhinitis and sinusitis. One having ordinary skill in the art would have been motivated to do this because ketaconazole was shown to be more effective than nystatin or amphotericin in the treatment of AFS by Bent III et al.

Applicant respectfully disagrees. Again, U.S. Patent No. 5,880,101 discloses treating 15 patients with pollen allergies and 8 patients with dust allergies. See, column 41, lines 5-17. At no point does U.S. Patent No. 5,880,101 disclose treating a patient with sinusitis, let alone a patient with both non-invasive fungus-induced rhinosinusitis and asthma. In addition, at no point

does U.S. Patent No. 5,880,101 teach or suggest that a person having ordinary skill in the art should treat a patient having both non-invasive fungus-induced rhinosinusitis and asthma. In fact, U.S. Patent No. 5,880,101 never mentions sinusitis, let alone non-invasive fungus-induced rhinosinusitis.

Even assuming for the sake of argument that U.S. Patent No. 5,880,101 somehow suggests that a person having ordinary skill in the art should treat a patient having both non-invasive fungus-induced rhinosinusitis and asthma, U.S. Patent No. 5,880,101 fails to provide a person having ordinary skill in the art with a reasonable expectation of success in achieving the successful treatment of a patient having both non-invasive fungus-induced rhinosinusitis and asthma. For example, U.S. Patent No. 5,880,101 does not provide any information regarding the successful treatment of patients with sinusitis, let alone patients with both non-invasive fungus-induced rhinosinusitis and asthma.

The Horner *et al.* reference and the Bent and Kuhn reference fail to correct the deficiencies of U.S. Patent No. 5,880,101. The Horner *et al.* reference is a review article that describes fungal allergens. At no point does the Horner *et al.* reference disclose the treatment of patients with both non-invasive fungus-induced rhinosinusitis and asthma. The Bent and Kuhn reference reports the *in vitro* susceptibility of fungal organisms to antifungal agents. At no point does the Bent and Kuhn reference disclose the treatment of patients with both non-invasive fungus-induced rhinosinusitis and asthma as presently claimed. In fact, the only antifungal treatment results disclosed in the Bent and Kuhn reference indicate that topical irrigations are unsuccessful at treating allergic fungal sinusitis. Specifically, the second sentence of the second complete paragraph on page 1333 of the Bent and Kuhn reference states "[i]n the early phases of this study we attempted intraoperative and postoperative topical irrigations with fluconazole without success." Thus, taken together, the combination of cited references does not render the presently claimed invention obvious.

In addition, Applicant respectfully disagrees with the Examiner's characterization of the Bent and Kuhn reference. In particular, the Examiner stated that "ketaconazole was shown to be more effective than nystatin or amphotericin in the treatment of AFS." At no point does the Bent

and Kuhn reference disclose the successful use of an antifungal agent to treat allergic fungal sinusitis. Moreover, at no point does the Bent and Kuhn reference disclose that ketaconazole was shown to be more effective than nystatin or amphotericin in the treatment of allergic fungal sinusitis. In fact, the only antifungal treatment results disclosed in the Bent and Kuhn reference indicate that topical irrigations are unsuccessful.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 76, 89, 122, 123, 127-129, 135-137, 144, 194-214, and 216-243 under 35 U.S.C. § 103(a).

The Examiner rejected claims 95 and 215 under 35 U.S.C. § 103(a) as being unpatentable over the Stankov reference (WO 96/00576) either alone or in view of the Horner *et al.* reference (*Clinical Microbiology Reviews*, 8(2):161-179 (1995)) and the Bent and Kuhn reference (*Laryngoscope*, 106:1331-1334 (1996)) and further in view of either the McCaffrey *et al.* reference (U.S. Patent No. 5,679,648) or the Haria *et al.* reference (*Drugs*, 51(4):585-620 (1996)). After acknowledging that the Stankov reference does not disclose itraconazole, the Examiner stated that the Bent and Kuhn reference teaches that "itraconazole was almost as effective as nystatin in the treatment of AFS," citing Table III of the Bent and Kuhn reference. The Examiner also stated that both the McCaffrey *et al.* reference and the Haria *et al.* reference teach that itraconazole is less toxic than amphotericin. The Examiner then concluded that:

> it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Stankov such that to employ itraconazole in addition to or instead of nystatin or amphotericin for the treatment of asthma, allergic rhinitis and sinusitis. One having ordinary skill in the art would have been motivated to do this because itraconazole was shown to be as effective as nystatin in the treatment of AFS by Bent III et al. and is less toxic than amphotericin as suggested by McCaffrey et al. or Haria et al.

Applicant respectfully disagrees. As stated above, the combination of U.S. Patent No. 5,880,101, the Horner *et al.* reference, and the Bent and Kuhn reference fails to render the presently claimed invention obvious. The McCaffrey *et al.* and Haria *et al.* references do not correct these deficiencies. Both the McCaffrey *et al.* reference and Haria *et al.* reference disclose

treating fungal infections. At no point do these references teach or suggest treating a patient having both non-invasive fungus-induced rhinosinusitis and asthma as presently claimed.

Thus, taken together, the combination of cited references does not render the presently claimed invention obvious.

Again, Applicant respectfully disagrees with the Examiner's characterization of the Bent and Kuhn reference. In particular, the Examiner stated that "itraconazole was almost as effective as nystatin in the treatment of AFS," citing Table III. Table III reports the *in vitro* susceptibility data. Table III does not report that itraconazole is almost as effective as nystatin in treating allergic fungal sinusitis. At no point does the Bent and Kuhn reference disclose the successful use of an antifungal agent to treat allergic fungal sinusitis. In fact, the only antifungal treatment results disclosed in the Bent and Kuhn reference indicate that topical irrigations are unsuccessful. See, second sentence of the second complete paragraph on page 1333.

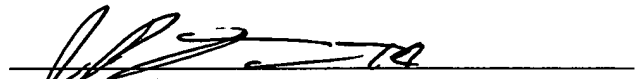
In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 95 and 215 under 35 U.S.C. § 103(a).

CONCLUSION

Applicant submits that claims 70-120, 122, 123, 127-129, 135-137, 143-145, 194-243, and 366-367 are in condition for allowance, which action is requested. The Examiner is invited to call the undersigned agent at the telephone number below if such will advance prosecution of this application. The Commissioner is authorized to charge any fees or credit any overpayments to Deposit Account No. 06-1050.

Respectfully submitted,

Date: March 1, 2004



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